Microorganisms for the Production of Lactic Acid and Organic Lactates

Christine Idler, Joachim Venus, and Birgit Kamm

Contents

Abstract Biorefineries consider lactic acid as one of the most promising platform chemicals which are being extensively used in a wide range of food and nonfood applications. Since lactic acid is produced via biotechnological processes, the microbial strains are in the focus of interest, besides all the other aspects of raw materials, fermentation mode, etc.

Microorganisms, which are able to produce lactic acid and organic lactates, are systematically classified and morphologically and biochemically characterized, and their different metabolic pathways for the formation of various lactic acid

C. Idler (✉) • J. Venus
Department of Bioengineering, Leibniz-Institute for Agricultural Engineering Potsdam-Bornim, Max-Eyth-Allee 100, 14469 Potsdam, Germany
e-mail: cidler@atb-potsdam.de

B. Kamm
Research Institute Bioactive Polymer Systems and Brandenburg Technical University Cottbus-Senftenberg, 14513 Teltow, Brandenburg, Germany

B. Kamm (ed.), *Microorganisms in Biorefineries*, Microbiology Monographs 26,
DOI 10.1007/978-3-662-45209-7_9

enantiomers are described in detail. The genera *Lactobacillus* and *Bifidobacterium* are regarded as well as the order of the Bacillales. In addition, the important individual yeasts, moulds and other bacteria were also characterized.

The present review work is summarized on the fermentation systems used for the biotechnological production, the various raw materials and applications of lactic acid and organic lactates. Future developments in this area with respect to the strain selection and modifications, genetic-engineering approaches, carbohydrate sources and their pretreatment, fermentation techniques and the downstream processing options are discussed.

Abbreviation

G + C	Guanine + cytosine
LA	Lactic acid
LAB	Lactic acid bacteria
PLA	Polylactic acid
ssp.	Subspecies

1 Introduction

The biotechnological production of lactic acid (2-hydroxypropionic acid) as an example of a platform chemical for the subsequent processing (e.g. into PLA) is carried out in technical reactors by using a suitable strain. LA can be produced by several microorganisms classified into bacteria, fungi, yeast, cyanobacteria and algae (Abdel-Rahman et al. 2013; Thongchul 2013). Besides the wide group of *Lactobacillus* (Antonio et al. 1996; Hofvendahl and Hahn-Hägerdahl 1997; Berry et al. 1999; Fu and Mathews 1999; Kwon et al. 2001), other bacteria like *Bacillus* (Payot et al. 1999; Danner et al. 2002; Patel et al. 2004), *Enterococcus* (Walczak et al. 2012), *Lactococcus* (Ramchandran et al. 2012), *Pediococcus* (Zhao et al. 2013b), *Streptococcus* (Tang et al. 2013) and filamentous fungi (Martak et al. 2003), especially *Rhizopus oryzae* (Yin et al. 1997; Bai et al. 2004), were also used as production strains. These microorganisms convert easily monosaccharides like glucose or fructose into cell mass and LA. LA formation and cell growth are closely coupled in LA fermentation (Zacharof and Lovitt 2013). An overview about the utilization of different renewable resources for LA fermentation, other microorganisms and yields depending on several process parameters was given by Hofvendahl and Hahn-Hägerdal (2000) and Castillo Martinez et al. (2013).

Whereas the fermentation of glucose can be carried out efficiently, the bioconversion of the pentose fraction out of lignocellulosic feedstocks and residues presents a challenge. A lot of attention has therefore been focused on genetically engineering strains that can efficiently utilize both glucose and pentose and convert them to useful compounds. The metabolic engineering objectives so far have

focused on higher yields, productivities and expanding the substrate and product spectra (Aristidou and Penttilä 2000; Hua et al. 2006; Singh et al. 2006; Ilmen et al. 2007; Adler et al. 2012).

For the industrial production of L-(+)-LA, it is necessary to provide cheap carbon sources that can be easily metabolized by lactic acid bacteria (LAB) and to obtain the optimal conditions of fermentation with higher yields and production rates (John et al. 2007).

The different microbes have achieved one or more improvements over the others, such as a broader substrate range, improved yield and productivity, reduction of nutritional requirements or improved optical purity of LA (Abdel-Rahman et al. 2013). In view of the above-mentioned several complex substrates, also the use of mixed cultures in fermentation may provide useful combinations of metabolic pathways for the utilization of complex raw materials containing a mixture of carbohydrates (Cui et al. 2011; Trontel et al. 2011; Secchi et al. 2012). Several genetic-engineering approaches have been exploited in order to improve performance, LA yield and optical purity by various microbial producers (Nagamori et al. 2013; Wu et al. 2013; Zhao et al. 2013a). An extensive review by Okano et al. (2010) provides a broad collection of genetically engineered microorganisms for LA production including their characteristics and applicability for fermentation processes, respectively.

2 Lactic Acid-Forming Bacteria

Important LA-forming bacteria include the genera *Lactobacillus* and *Bifidobacteria*. Also the genera *Bacillus*, *Lactococcus*, *Streptococcus*, *Pediococcus* and *Enterococcus* are able to produce LA. There are also reports about the LA fermentation by some yeast and fungi.

2.1 The Genus Lactobacillus

Lactobacillus (*L.*) is a very heterogeneous genus, comprising species with a large diversity of phenotypic, biochemical and physiological features. More than 70 species are recognized, and all are able to convert carbohydrates into LA. The most important LA-forming bacteria belong to this genus. These include *L. acidophilus, L. brevis, L. casei, L. delbrueckii, L. fermentum, L. helveticus, L. plantarum, L. paracasei* and *L. rhamnosus*.

Table 1 Characteristics of the genus *Lactobacillus*

Classification[a]	Kingdom	Bacteria
	Phylum	Firmicutes
	Class	Bacilli
	Order	Lactobacillales
	Family	Lactobacillaceae
	Genus	*Lactobacillus*
Type species	*L. delbrueckii*	
Habitats	Dairy products, silage, water, soil, sewage, part of the normal flora of human and many animals	
Characteristics	Gram positive, non-spore forming, catalase negative, motile or immotile, facultative anaerobic	
Morphology	Long and slender or bent rods or coccobacilli common in chains Motile by peritrichous flagella	
Metabolism	Obligately saccharolytic, end products: lactate, acetate, formate, succinate, ethanol, CO_2	
Fermentation types	Obligate homofermentative: *L. acidophilus, L. delbrueckii* Obligate heterofermentative: *L. brevis, L. fermentum* Facultative heterofermentative: *L. casei, L. rhamnosus*	
Growth conditions	$T_{opt.}$: 30–40 °C (2–53 °C) $pH_{opt.}$: 5.5–6.2, tolerant < 4 Requirements: individually various complex nutritional requirements for peptides, amino acids, nucleotides, vitamins and fermentable carbohydrates	
Pathogenicity	No or in rare case, e.g. *L. rhamnosus,* biosafety level 2[b]	
DNA GC content	32.5–55 mol %	
Remarks	Than other LAB more resistant to acid conditions	

[a]Hammes and Hertel (2009)
[b]Directive 89/391/EEC (2000)

2.1.1 Short Characteristics of the Genus *Lactobacillus*

The genus can be divided into three subgroups based on their type of fermentation: obligate homofermentative, obligate heterofermentative and facultative heterofermentative. Important features of this genus are summarized in Table 1.

2.1.2 Carbohydrate Fermentation of Lactobacilli

The metabolism of carbohydrate utilization depends both on the kind of the sugar (e.g. hexoses, pentoses) and from the type of fermentation by the LAB. General, the fermentation types differ in the utilization of hexoses and pentoses.

Fermentation of Hexoses

Obligate Homofermentative LAB

In principle the obligate homofermentative LAB converted hexoses to lactate by the Embden-Meyerhof-Parnas (EMP) glycolytic pathway (Fig. 1) (Wood 1961; Kandler 1983; von Wright and Axelsson 2012).

Glucose is first broken down in glycolysis to pyruvate. Pyruvate is reduced by the enzyme lactate dehydrogenase to lactate, which is present under physiological conditions in dissociated lactate ions and protons. During the glycolysis of glucose or fructose per molecule, two molecules lactate and ATP are formed, so that the sum of the equation homofermentative LA fermentation is

$$C_6H_{12}O_6 + 2\,ADP \rightarrow 2\,C_3H_6O_3 + 2\,ATP$$

Pentoses and gluconate were not fermented by this pathway because of lack of enzyme phosphoketolase. This type of fermentation includes some species of the genus *Lactobacillus*. The important LA producers in this genus are *L. acidophilus* and *L. delbrueckii* (Hofvendahl and Hahn-Hägerdal 2000; Kwon et al. 2001).

Obligate Heterofermentative LAB

The pathway of obligate heterofermentative LA fermentation is formed by LAB, which had a lack of enzyme aldolase. This enzyme is required for the glycolysis of fructose-1,6-bisphosphate into the two phosphotriose dihydroxyacetone and glyceraldehyde. This type of fermentation includes organisms of the genera *Leuconostoc, Weissella* and *Oenococcus* as well as some species of the genus *Lactobacillus* (Hammes et al. 1991; Hammes and Vogel 1995). Important obligate heterofermentative LA producers are *L. brevis, L. fermentum* and *L. reuteri*. These bacteria can degrade hexoses in the phosphogluconate pathway (Fig. 2) to lactate, ethanol and CO_2 or furthermore to acetate.

During the fermentation of glucose per molecule, one molecule lactate and ATP are formed, so that the sum of the equation of heterofermentative LA fermentation is

$$C_6H_{12}O_6 + ADP \rightarrow C_3H_6O_3 + C_2H_5OH + CO_2 + ATP$$

Other hexoses (such as mannose or fructose) enter the pathway as either glucose-6-phosphate or fructose-6-phosphate. Fructose, however, is reduced not only to lactate and CO_2 but also to mannitol and acetate:

$$3\,C_6H_{12}O_6 + H_2O + 2\,ADP \rightarrow C_3H_6O_3 + 2\,C_6H_{14}O_6 + C_2H_4O_2 + CO_2 + 2\,ATP$$

For the fermentation of galactose, there are two different pathways, depending on the form it enters in the cells (von Wright and Axelsson 2012). If galactose enters

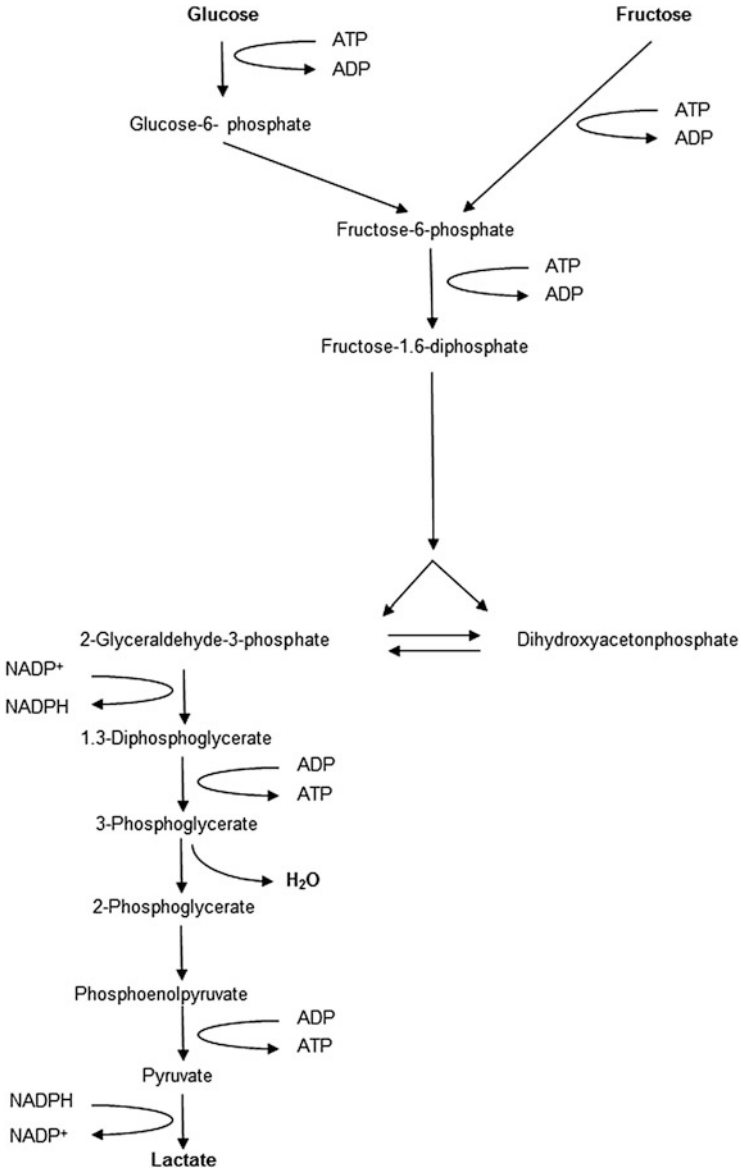

Fig. 1 Fermentation of hexoses in obligate homofermentative LAB, EMP pathway

the cells as galactose-6-phosphate, it will ferment also to pyruvate however via the tagatose-6-phosphate pathway (Bisset and Anderson 1974) (Fig. 3a). As a free galactose, imported in the cells by a specific permease, it will ferment via glycolysis to pyruvate by the so-called Leloir pathway (Kandler 1983) (Fig. 3b).

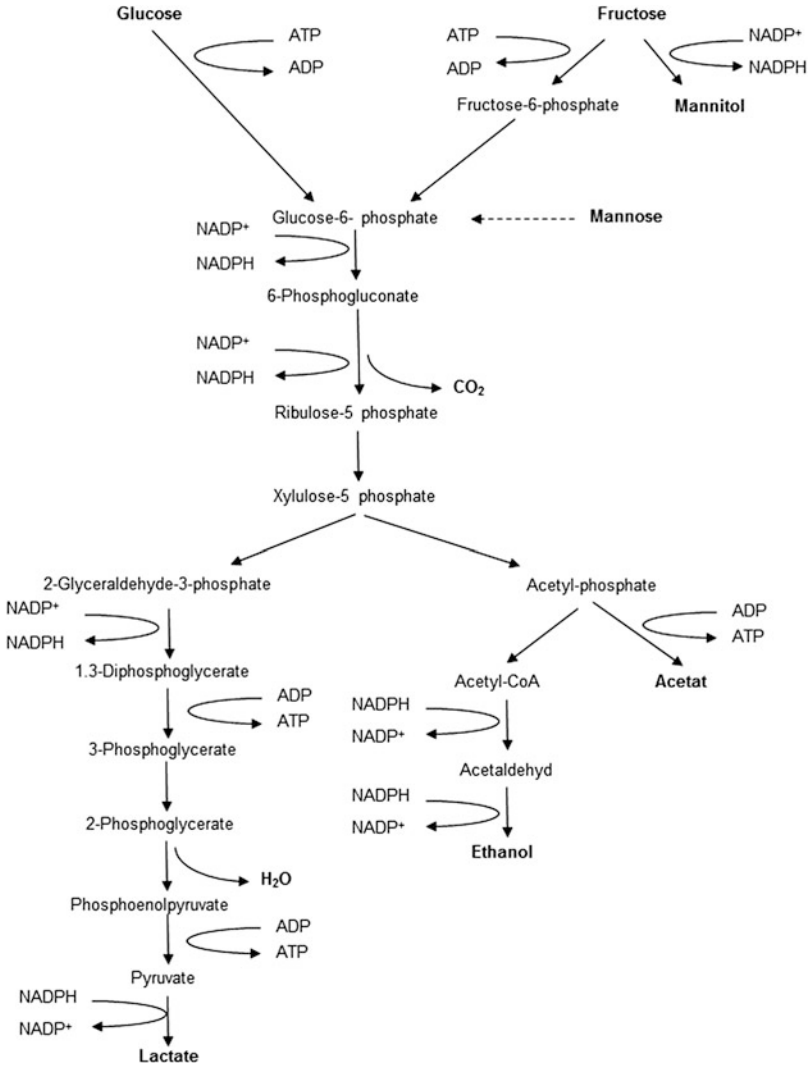

Fig. 2 Fermentation of hexoses in heterofermentative LAB, phosphogluconate pathway

Fermentation of Pentoses

Many LAB are able to ferment pentoses. They can only ferment heterofermentatively by entering the phosphogluconate pathway as either ribulose-5 phosphate or xylulose-5 phosphate (Kandler 1983) (Fig. 4). Pentoses (such as arabinose, ribose, xylose) are converted into lactate and acetate; CO_2 is not produced. The sum of the equation is

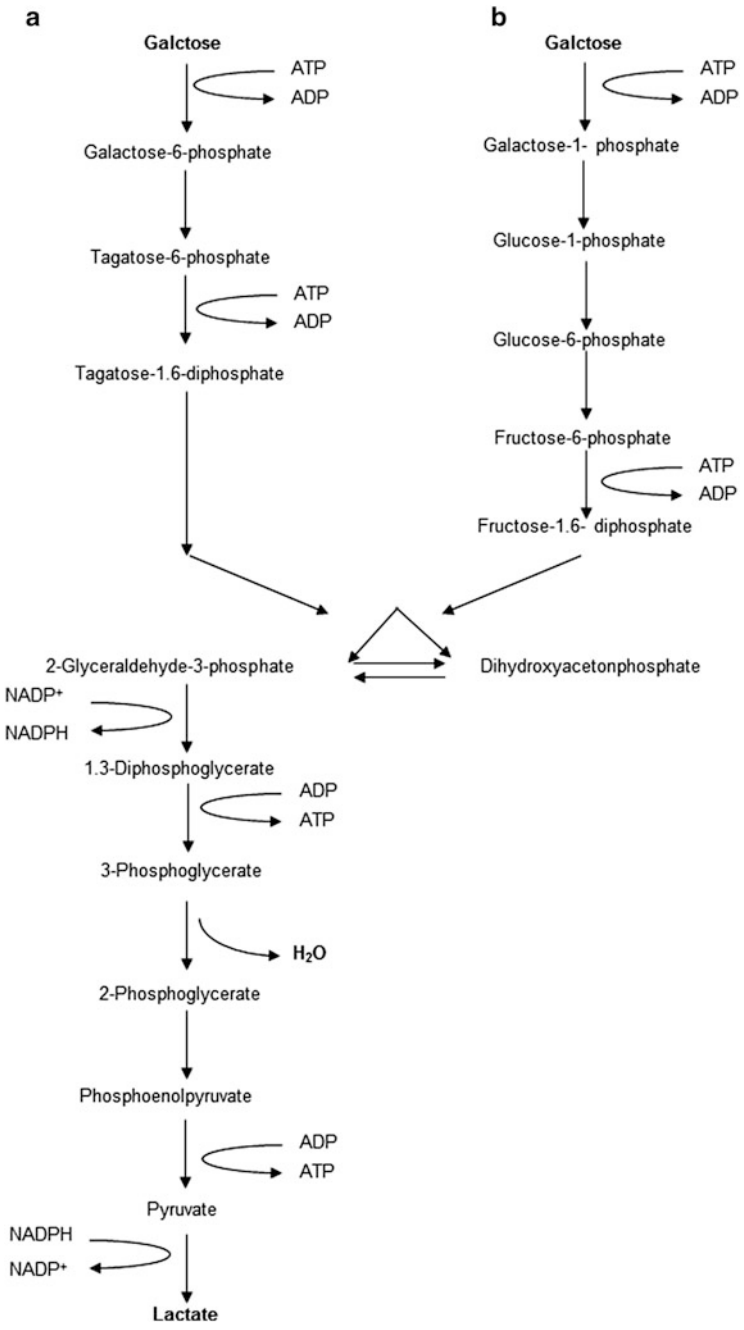

Fig. 3 Fermentation of galactose in LAB, Leloir pathway

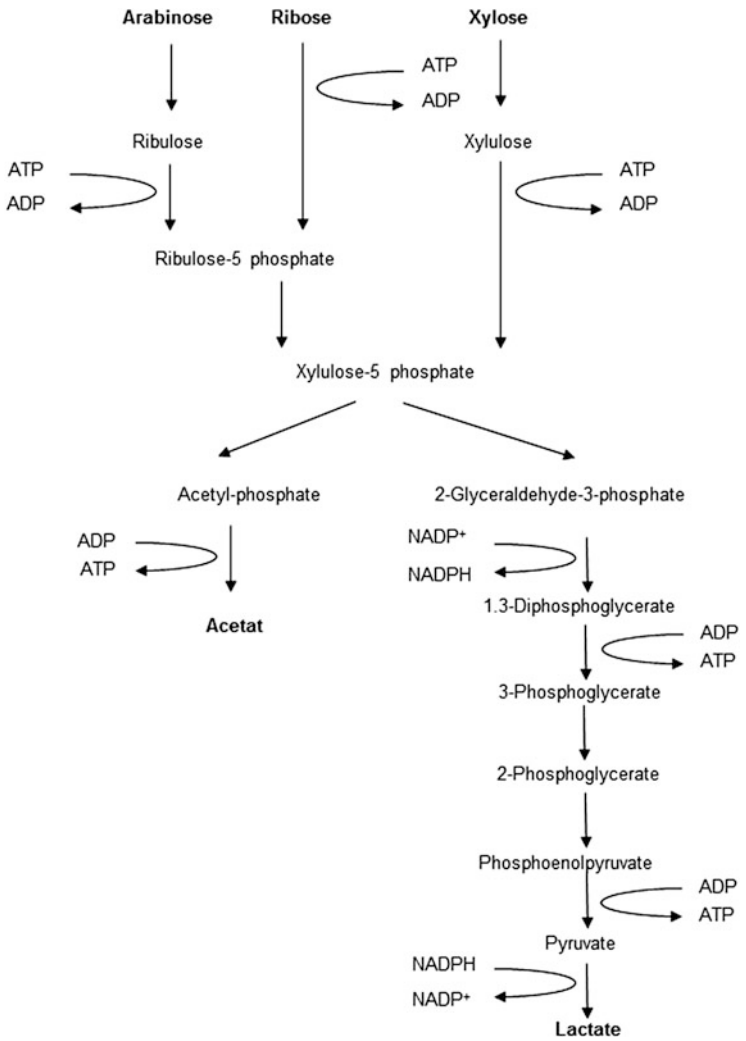

Fig. 4 Fermentation of various pentoses in LAB

$$C_5H_{10}O_5 + 2\,ADP \rightarrow C_3H_6O_3 + C_2H_4O_2 + 2\,ATP$$

However, there are reports of homofermentative fermentation of pentoses by engineered strains of *L. plantarum* (Okano et al. 2009a, b).

Facultative Heterofermentative LAB

LAB, which can ferment hexoses and pentoses, belong to the group of facultative heterofermentative LAB. Hexoses are fermented by the EMP glycolytic pathway to

lactate. Under glucose limitation some species can produce also ethanol, acetic acid and formic acid (Hammes and Hertel 2009). Pentoses enter this pathway and are fermented to LA and acetic acid. The important LA producers belong to this fermentation type, e.g. *L. casei, L. plantarum* and *L. paracasei*.

Fermentation of Other Important Carbohydrates

For the production of LA, the most important carbohydrates are the disaccharides lactose, maltose and sucrose. In principle they are split enzymatically into their monosaccharide, and then they enter the various pathways.

Lactose can enter the cells in two ways, either by means of a specific permease or as lactose-6-phosphate (von Wright and Axelsson 2012). In the first case, lactose is split into glucose and galactose, which can enter the major fermentation pathway (e.g. *Streptococcus thermophilus*). In the second case, lactose-6-phosphate is cleaved to glucose and galactose-6-phosphate. While glucose is processed by the glycolytic pathway, the galactose-6-phosphate enters the tagatose-6-phosphate pathway (e.g. *Lactococcus lactic*). In some cases both systems can coexist (Wood and Holzapfel 1995; von Wright and Axelsson 2012).

The fermentation of maltose is known; in lactococci the permease system is active (Sjöberg and Hahn-Hägerdahl 1989), while in various strains of *L. sanfranciscensis*, maltose is converted to glucose-1-phosphate and glucose (von Wright and Axelsson 2012).

In general, sucrose enters the cells also by a specific permease system, and it is split into glucose and fructose. Also it was reported that lactococci can convert lactose into glucose-6-phosphate and fructose (von Wright and Axelsson 2012).

Starch is fermented only by very few homofermentative species such as *L. amylophilus* (Altaf et al. 2006; Vishnu et al. 2006), *L. manihotivorans* (Morlon-Guyot et al. 1998; Ohkouchi and Inoue 2006) and *L. amylovorus* (Zhang and Cheryan 1991; Hammes and Hertel 2009). However, of these species *L. amylophilus* and *L. manihotivorans* are important for the production of LA (Altaf et al. 2007; Yen and Kang 2010; Son and Kwon 2013).

It is reported that the strain *Lactobacillus plantarum SW14* has a potential for LA production directly from cassava starch under laboratory conditions (Bomrungnok et al. 2012). Also *Enterococcus faecium* was already described for the direct fermentation of starch containing feedstocks (Shibata et al. 2007; Nolasco-Hipolito et al. 2012).

2.1.3 Enantiomers of LA

An asymmetric C-atom LA exists in two enantiomeric forms L (+) and D (−) and in a racemic form (DL). The stereoisomeric composition of the formed LA by the various species of lactobacilli is enzymatically determined. The configuration of the LA L (+) or D (−) depends on the stereospecificity of the lactate dehydrogenase in

the cells. Racemate (DL) formed either when D-(−)- and L-(+)-dehydrogenases are present in the same cells or when an inducible lactate racemate reacts with a constitutive L-(+)-lactate dehydrogenase (Hammes and Hertel 2009).

However Setter and Stetter and Kandler (1973) reported that the D-(−)-lactate formers produce D-(−)-lactate exclusively, whereas all L-(+)-lactate formers always produce a few percent of the other isomer. This is caused by the presence of an NAD-dependent D-lactate dehydrogenase of very low activity.

2.1.4 Characteristics of the Most Important Lactic Acid Producers

For the selection of strains for the LA production, the fermentation type, the fermented carbohydrates and the temperature of growth are very important. These typical facts for the most used LA producers in the genus *Lactobacillus* are summarized separately in Tables 2, 3 and 4 after the formation of the various LA enantiomer.

2.2 The Genus Bifidobacterium

There are many references of the use of bifidobacteria for LA production. Many investigations have shown that bifidobacteria promote health preferably via their application in the food industry (Shene et al. 2005; Popa and Ustunol 2011). From that perspective the interest has been focused more on the fermentation performance in combination with typical carbohydrates containing foodstuff (Buruleanu et al. 2011; Watson et al. 2012) than an industrial LA production (Li et al. 2008). In the genus *Bifidobacterium* (*B.*), *B. adolescentis, B. animalis, B. bifidum, B. breve, B. longum* and *B. thermophilum* are important LA producers.

2.2.1 Short Characteristics of the Genus *Bifidobacterium*

Important features of this genus are summarized in Table 5.

2.2.2 Carbohydrate Fermentation

Bifidobacteria ferment various types of sugars. Lactose, galactose and sucrose are metabolized by a large number of species. The bacteria lack enzyme aldolase (fructose-1,6-bisphosphate-aldolase), like other heterofermentative LAB, but they metabolize sugars via their own complicated pathway so-called *bifid shout* (De Vries and Stouthamer 1967) (Fig. 5). Hexoses are degraded via phosphoric esters of the hexoses, erythrose, glyceraldehyde and pentoses. At two sites acetyl-phosphate is cleaved and 2-glyceraldehyde-3-phosphate is formed. This is

Table 2 Characteristics of *Lactobacillus* species produced L-(+)-LA

Species	Fermentation type	Growth (°C)	Relevant fermented carbohydrates[a]												
		15/45	Arabinose	Cellobiose	Fructose[b]	Galactose[b]	Glucose[b]	Lactose	Maltose[b]	Mannose	Raffinose	Ribose	Sucrose	Starch	Xylose
L. amylophilus	A	+/−	−	−	+	+	+	−	+	+	−	−	−	+	−
L. casei	C	+/−	−	+	+	+	+	d	+	+	−	+	+	ND	−
L. paracasei ssp. *paracasei*	C	+/d	−	+	+	+	+	+	+	+	−	+	+	−	−
L. rhamnosus	C	+/+	d	+	+	+	+	+	+	+	−	+	+	−	−
L. manihotivorans	A	+/+	−	+	+	+	+	+	+	+	+	−	+	+[c]	−
L. salivarius ssp. *salivarius*[d]	A	−/+	−	−	+	+	+	+	+	−	+	−	+	−	−
L. salivarius ssp. *salicinius*[e]	A	−/+	−	−	+	+	+	+	+	−	+	−	+	−	−

A, obligate homofermentative; C, facultative heterofermentative; +, 90 % or more of strains are positive; −, 90 % or more of strains are negative; d, 11–89 % of strains are positive

[a]Hammes and Hertel (2009)

[b]Kandler and Weiss (1986)

[c]Son and Kwon (2013)

[d]Ferments rhamnose but not salicin and esculin

[e]Ferments salicin and esculin but not rhamnose

Table 3 Characteristics of *Lactobacillus* species produced D-(−)-LA

Species	Fermentation type	Growth (°C)	Relevant fermented carbohydrates[a]												
		15/45	Arabinose	Cellobiose	Fructose[b]	Galactose[b]	Glucose[b]	Lactose	Maltose	Mannose	Raffinose	Ribose	Sucrose	Starch	Xylose
L. coryniformis ssp. *coryniformis*	C	+/−	−	−	+	ND	+	+	−	ND	d	−	+	ND	−
L. coryniformis ssp. *torquens*	C	+/−	−	−	+	ND	+	+	−	ND	−	−	+	ND	−
L. delbrueckii ssp. *delbrueckii*	A	−/+	−	−	+	−	+	−	d	+	−	−	+	ND	−
L. delbrueckii ssp. *bulgaricus*	A	−/+	−	d	+	−	+	+	−	−	−	−	−	ND	−
L. delbrueckii ssp. *lactis*	A	−/+	−	d	+	d	+	+	+	+	−	−	+	ND	−

A, obligate homofermentative; C, facultative heterofermentative; +, 90 % or more of strains are positive; −, 90 % or more of strains are negative; d, 11–89 % of strains are positive

ND no data available

[a]Hammes and Hertel (2009)

[b]Kandler and Weiss (1986)

Table 4 Characteristics of *Lactobacillus* species produced DL-LA

Species	Fermentation type	Growth (°C)	Relevant fermented carbohydrates[a]												
		15/45	Arabinose	Cellobiose	Fructose[b]	Galactose[b]	Glucose[b]	Lactose	Maltose	Mannose	Raffinose	Ribose	Sucrose	Starch	Xylose
L. acidophilus	A	−/+	−	+	+	+	+	+	+	+	d	−	+	ND	−
L. amylovorus	A	−/+	−	+	+	+	+	−	+	+	−	−	+	+	−
L. brevis	B	+/−	+	−	+	d	+	ND	+	−	d	+	d	ND	d
L. fermentum	B	−/+	d	d	+	+	+	+	+	d	+	+	+	ND	d
L. helveticus	A	−/+	−	−	+	+	+	+	d	d	−	−	−	ND	−
L. plantarum ssp. *plantarum*	C	+/−	d	+	+	+	+	+	+	+	+	+	+	[c]	d
L. reuteri	B	−/+	+	−	+	+	+	+	+	−	+	+	+	ND	−

A, obligate homofermentative; B, obligate heterofermentative; C, facultative heterofermentative; +, 90 % or more of strains are positive; −, 90 % or more of strains are negative; d, 11–89 % of strains are positive

ND no data available

[a]Hammes and Hertel (2009)

[b]Kandler and Weiss (1986)

[c]Only some strains (Giraud et al. 1994)

Table 5 Characteristics of the genus *Bifidobacterium*

Classification[a]	Kingdom	Bacteria
	Phylum	Actinobacteria
	Class	Actinobacteria
	Subclass	Actinobacteridae
	Order	Bifidobacteriales
	Family	Bifidobacteriaceae
	Genus	*Bifidobacterium*
Synonyms[b]	Before the 1960s, *Bifidobacterium* species were collectively referred to as *Lactobacillus bifidus*	
Habitats	Human, animal and insect intestine, sewage	
Characteristics	Gram positive, non-spore forming, catalase negative, immotile, mainly anaerobe	
Morphology	Rods of various shapes, bifid morphology of the cells that means long cells with slight bends	
Metabolism	Obligately sacchoroclastic, main products: lactate, acetate	
Fermentation types	Carbohydrate processed via a special fructose-6-phosphate phosphoketolase pathway	
Growth conditions	$T_{opt.}$: 37–41 °C (25–47 °C) $pH_{opt.}$: 6.5–7.0, no growth at 4.5–5.0 and 8.0–8.5[c] Requirements: complex biological substances, as casein, bovine serum albumin digest, casein digest, hog gastric mucin or yeast extract	
Pathogenicity	No	
DNA G + C content	55–67 mol%	
Remarks[d]	Species and strains differ in the sensitivity to oxygen, important probiotics and used in the food industry	

[a]Stackebrandt et al. (1997)
[b]Sgorbati et al. (1995)
[c]Scardovi (1986)
[d]De Vries and Stouthamer (1969)

metabolized by the Embden-Meyerhof-Parnas pathway to L-(+)-lactic and acetic acid in the ratio 2:3 (Sgorbati et al. 1995). Gas is not produced. This pathway has a 25 % higher yield of ATP (2.5 moles per mole of glucose) as the homofermentative LA fermentation (2 moles per mole of glucose). The sum of the fermentation of glucose is

$$2\,C_6H_{12}O_6 \rightarrow 2C_3H_6O_3 + 3C_2H_4O_2 + 5\,ATP$$

Galactose is fermented by the Leloir pathway (Fig. 3) because the enzymes for this are basically available in glucose-grown cells. On this pathway gas is formed (Scardovi 1986).

The fermented carbohydrates from the most important species of the genus *Bifidobacterium* are summarized in Table 6.

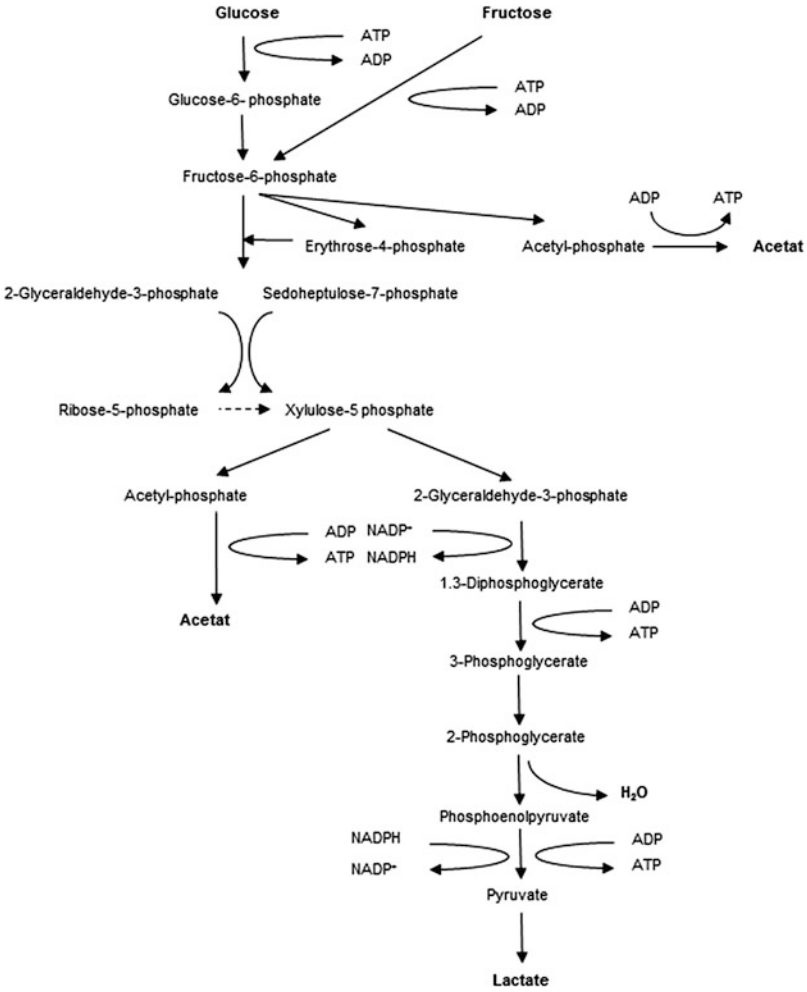

Fig. 5 Fermentation of glucose and fructose by bifidobacteria, *bifid shout*

2.3 The Order Bacillales

LA production is traditionally associated with non-spore-forming bacteria. In addition to these organisms, a number of LA-producing spore-forming bacteria have been described. They are allocated to the genera *Bacillus* and *Sporolactobacillus*. The most important LA producer in the genus *Bacillus* is the species *Bacillus* (*B*.) *coagulans* and in the genus *Sporolactobacillus* (*S*.) the species *S*. *inulinus* and *S*. *laevolacticus*.

Table 6 Fermentation of carbohydrates by important species of the genus *Bifidobacterium*

	Relevant fermented carbohydrates[a]												
Bifidobacterium	Arabinose[b]	Cellobiose[b]	Fructose	Galactose	Glucose	Lactose[b]	Maltose	Mannose	Raffinose[b]	Ribose[b]	Sucrose	Starch	Xylose
B. adolescentis	+	+	+	+	+	+	+	d	+	+	+	+	+
B. animalis	+	d	+	+	+	+	+	d	+	+	+	+	+
B. bifidum	+	–	+[e]	+	+	+	–	–[d]	–	–	d[d]	–	–
B. breve	–	d	+	+	+	+	+	+	+	+	+	–	–
B. longum	+	–	+	+	+	+	+	d	+	+	+	–	d
B. thermophilum	–	d	+	+	+	d	+	–[d]	+	–	+	+	–

+, 90 % or more of strains are positive; –, 90 % or more of strains are negative; d, 11–89 % of strains are positive

[a]Scardovi (1986)

[b]Sgorbati et al. (1995)

[c]Few strains do not ferment this sugar

[d]Few strains ferment this sugar

[e]Some strains are weak fermenters

Table 7 Characteristics of the genus *Sporolactobacillus*

Classification[a]	Kingdom	Bacteria
	Phylum	Firmicutes
	Class	Bacilli
	Order	Bacillales
	Family	Sporolactobacillaceae
	Genus	*Sporolactobacillus*
Type strain	*Sporolactobacillus inulinus*	
Habitats	Soil, canned food, compost, chicken feed, sea mud, plants	
Characteristics	Gram positive, endospore forming, facultative anaerobic or microaerophilic, catalase negative, motile	
Morphology	Straight rods singly, in pairs or rarely in short chains, long peritrichous flagella, oval spore shape	
Growth conditions[a]	$T_{opt.}$: 35 °C (25–40 °C) $pH_{opt.}$: 5.5 Requirements: carbohydrates, no growth in nutrient media	
Fermented carbohydrates[a]	Galactose, lactose, glucose, fructose, mannose, sucrose, maltose, trehalose, starch (Table 8)	
Fermentation type	Homofermentative	
LA enantiomer	D (−) or DL	
Pathogenicity	No	
DNA G + C content[a]	43–50 mol%	
Remarks[b]	Strains of the species may appear gram stain negative when the cells are older, e.g. when they enter the stationary phase	

[a]Ludwig et al. (2009)
[b]Fritze and Claus (1995)

2.3.1 The Genus *Sporolactobacillus*

The species *S. inulinus* and *S. laevolacticus* belong to the genus *Sporolactobacillus*, the only genus of the family of Sporolactobacillaceae. Important features of this genus are summarized in Table 7.

The species *S. inulinus* (Fukushima et al. 2004; Wang et al. 2011; Zheng et al. 2012) and *S. laevolacticus* (Mimitsuka et al. 2012; Li et al. 2013) are important D-(−)-LA producers particularly because of their ability to metabolize starch and inulin (Table 8).

2.3.2 *Bacillus coagulans*

A lot of species of the genus *Bacillus* (*B.*) are known for producing LA such as *B. lentimorbus*, *B. popilliae*, *B. smithii*, *B. stearothermophilus*, *B. licheniformis* and *B. subtilis* (Thomas et al. 1979; Claus and Berkeley (1986) Fritze and Claus 1995; Abdel-Rahman et al. 2013). One of the most important species forming LA is

Table 8 Fermented carbohydrates of important species of the genus *Sporolactobacillus*

Species	Relevant fermented carbohydrates													
	LA enantiomer	Arabinose	Cellobiose	Fructose	Galactose	Glucose	Inulin	Lactose	Maltose	Mannose	Raffinose	Ribose	Starch	Xylose
S. inulinus	D	–	–	ND	–	+	+	–	ND	No	+	–	+	–
S. laevolacticus	D	–	+	ND	+	+	+	+	ND	+	+	–	d	–

+, 90 % or more of strains are positive; –, 90 % or more of strains are negative; d, 11–89 % of strains are positive
ND no data available

Table 9 Characteristics of *B. coagulans*

Classification[a]	Kingdom	Bacteria
	Phylum	Firmicutes
	Class	Bacilli
	Order	Bacillales
	Family	Bacillaceae
	Genus	*Bacillus*
	Species	*B. coagulans*
First isolation	Hammer 1905, spoiled canned milk	
Synonyms[b]	*B. calidolactic, B. thermoacidurans, B. dextrolacticus, B. thermoacidificans, Lb. cereal*	
Habitats[a]	Soil, canned food, tomato juice, gelatin, milk, silage	
Characteristics	Gram positive, spore forming, facultative anaerobic, catalase positive, motile, facultative thermophilic	
Morphology	Rods, spores are oval or cylindrical and terminally or subterminally located, peritrichous flagella	
Growth conditions[a]	$T_{opt.}$: 50 °C (30–55 °C) $pH_{opt.}$: 7.0 (4–11) Requirements: simple, mineral salt medium with few nitrogen sources	
Fermented carbohydrates[a]	+: fructose, glucose, galactose, maltose, mannose, starch, trehalose, xylose d: arabinose, cellobiose, lactose, raffinose, ribose, sucrose	
Fermentation type	Heterofermentative	
LA enantiomer	L (+)	
Pathogenicity	No	
DNA G + C content[a]	44.3–50.3 mol%	
Remarks[c]	Strains of the species may appear gram stain negative when the cells are older, e.g. when they enter the stationary phase	

+, 90 % or more of strains are positive; d, 11–89 % of strains are positive
[a]Logan and de Vos (2009)
[b]Wood and Holzapfel (1995)
[c]Fritze and Claus (1995)

B. coagulans (Ou et al. 2011; Wang et al. 2012; Tashiro et al. 2013; Ma et al. 2014). Important features of this species are summarized in Table 9.

Glucose is mainly fermented to L-(+)-LA and smaller amounts of 2.3-butanediol, acetoin, acetic acid and ethanol (Fritze and Claus 1995). Some strains of *B. coagulans* are able to ferment hexoses and pentoses homolactic to L-(+)-LA (Wang et al. 2012; Ou et al. 2011).

2.4 *Other LA-Forming Microorganisms*

Besides the previously described species of the genera *Lactobacillus, Bifidobacteria, Bacillus* and *Sporolactobacillus*, there are a few bacteria of different systematic positions that are significant for forming LA. The most important bacteria are *Enterococcus faecium*, *Lactococcus lactis*, *Pediococcus acidilactici* and *Streptococcus thermophilus*. Yeasts and fungi are also of increasingly economic importance such as *Saccharomyces cerevisiae* and *Rhizopus oryzae*. Since over 10 years there are reports from LA-producing *E. coli* strains. Most of them are described as metabolically engineered strains for the production of LA (Chang et al. 1999; Dien et al. 2001; Baba et al. 2006; Kim et al. 2013).

2.4.1 *Enterococcus faecium*

Compared to other LA-producing microorganisms, *E. faecium* does not play a major role for the industrial application, but it was already described for the direct fermentation of starch containing feedstocks (Shibata et al. 2007; Nolasco-Hipolito et al. 2012). Important features of *E. faecium* are summarized in Table 10.

2.4.2 *Lactococcus lactis*

From the family of Streptococcaceae, the species *Lactococcus lactis* (*L. lactis*) and *Streptococcus thermophilus* are particularly very important for LA production. The species of the genus *Lactococcus* differ from the other LAB by their pH and by their salt and temperature tolerance for growth (Table 9). Among LAB, *L. lactis* is the most extensively studied regarding its physiology, metabolic pathways and regulatory mechanisms. Its genome was the first LAB genome to be completely sequenced (Oliveira et al. 2005). Important features of *L. lactis* are summarized in Table 11.

Among the subspecies of *L. lactis*, *L. lactis* ssp. *lactis* (John et al. 2007) and *L. lactis* ssp. *cremoris* are most important for the production of LA (Ramchandran et al. 2012; Mukisa et al. 2012). Fermented carbohydrates of the important species are arranged in Table 12.

It is reported in the literature that *L. lactis* produce LA as the sole metabolic product at high dilution rates during continuous cultivations or at high glucose concentrations during batch growth (Benthin 1994; Melchiorsen et al. 2002). In contrast, growth at low dilution rates in continuous conditions or at low concentrations of glucose in batch conditions results in a mixed-acid fermentation, where formate, ethanol and acetate are produced in a molar ratio of 2:1:1 (Melchiorsen et al. 2001).

Table 10 Characteristics of *E. faecium*

Classification[a]	Kingdom	Bacteria
	Phylum	Firmicutes
	Class	Bacilli
	Order	Lactobacillales
	Family	Enterococcaceae
	Genus	*Enterococcus*
	Species	*E. faecium*
First isolation	Orla-Jensen 1919	
Synonyms	*Streptococcus faecium*	
Habitats[b]	Gastrointestinal tract of mammals, birds, reptiles, food (raw milk, milk products), environment (plant, water)	
Characteristics	Gram positive, non-spore forming, facultative anaerobic, catalase negative (on blood agar same strains reveal pseudocatalase), immotile, alpha haemolytic or nonhaemolytic, anaerobic and aerobic metabolism	
Morphology	Ovoid cells, single, in pairs or chains	
Growth conditions	$T_{opt.}$ 35–37 °C (10–40 °C), survive 30 min. temperatures at 60 °C pH 4.6–9 Requirements: complexes such as brain heart infusion, blood, folic acid, some strains the same requirements such as LAB	
Fermented carbohydrates	+: cellobiose, fructose, glucose, galactose, lactose, maltose, mannose, ribose, starch, xylose[b] d: arabinose, raffinose, sucrose[a]	
Fermentation type	Homofermentative	
LA enantiomer	L (+)	
Pathogenicity	Human pathogenic, causing diseases such as neonatal meningitis	
DNA G + C content[a]	37.0–40.0 mol%	
Remarks[a]	Some strains are used as probiotics in animals, can produce enterotoxins (bacteriocin 31, enterotoxins A, B, P and 50)	

+, 90 % or more of strains are positive; d, 11–89 % of strains are positive
[a]Svec and Devriese (2009)
[b]Devriese and Pot (1995)

2.4.3 *Pediococcus acidilactici*

There have been not much applications published for *P. acidilactici* (Hofvendahl and Hahn-Hägerdal (2000), Giurca and Levin (1992, 1993)), but the new strain DQ2 has been recently described, which is characterized by high-temperature tolerance, high lignocellulose-derived inhibitor resistance and high LA production performance in combination with simultaneous saccharification and fermentation at high-solids loading of corn stover (Dao et al. 2013; Zhao et al. 2013b). Important features of *P. acidilactici* are summarized in Table 13.

Table 11 Characteristics of *L. lactis*

Classification[a]	Kingdom	Bacteria
	Phylum	Firmicutes
	Class	Bacilli
	Order	Lactobacillales
	Family	Streptococcaceae
	Genus	*Lactococcus*
	Species	*L. lactis*
	Subspecies	*L. lactis* ssp. *lactis*, *L. lactis* ssp. *cremoris*, *L. lactis* ssp. *hordniae*
First isolation	Joseph Lister (1873)	
Synonyms	*Bacterium lactis, Streptococcus lactis, Streptococcus cremoris*[b]	
Habitats	Raw milk, dairy products	
Characteristics	Gram stain positive, non-spore forming, facultative anaerobic, catalase negative, immotile	
Morphology	Ovoid cells, mostly in pairs, or in short chains	
Growth conditions	$T_{opt.}$: 30–40 °C (10–40 °C), no growth at 45 °C $pH_{opt.}$: 7.0 (tolerate 4.5) Requirements: individually various complex nutritional requirements for peptides, amino acids, vitamins and fermentable carbohydrate, phosphate, potassium, magnesium[c]	
Fermented carbohydrates	s. Table 12	
Fermentation type	Homofermentative	
LA enantiomer	L (+)	
Pathogenicity[d]	Absent or in rare case	
DNA G + C content[c]	33.8–36.8 mol%	
Remarks	Type strain of the genus *Lactococcus,* starter culture in the dairy industry, especially in the cheese manufacture, produced bacteriocin nisin, type of species of the genus	

[a]Teuber (2009)
[b]Teuber (1995)
[c]Oliveira et al. (2005)
[d]Teuber (2006)

2.4.4 *Streptococcus thermophilus*

The classification and nomenclature of streptococci have undergone significant changes over the years. In recent years, based on biochemical characteristics as well as RNA analysis, members of the genus *Streptococcus* have been reclassified into *Lactococcus*, *Vagococcus*, *Enterococcus* and *Streptococcus*. This genus includes both significant human and animal pathogens but also nonpathogenic species, in particular *S. thermophilus*, for the production of food (especially milk, milk products and cheese) and LA, particularly on lactose-rich substrates (Hofvendahl and Hahn-Hägerdal 2000; Pescuma et al. 2008; Secchi et al. 2012;

Table 12 Fermented carbohydrates in *L. lactis* subspecies (Teuber 2009)

Species	Relevant fermented carbohydrates												
	Arabinose	Cellobioe	Fructose	Galactose	Glucose	Lactose	Maltose	Mannose	Raffinose	Ribose	Sucrose	Starch	Xylose
Lactococcus lactis ssp. *lactis*	–	d	+	+	+	+	+	+	–	+	d	d	d
Lactococcus lactis ssp. *cremoris*	–	d	+	+	+	+	–	+	–	–	d	–	d

+, 90 % or more of strains are positive; –, 90 % or more of strains are negative; d, 11–89 % of strains are positive

Table 13 Characteristics of *P. acidilactici*

Classification[a]	Kingdom	Bacteria
	Phylum	Firmicutes
	Class	Bacilli
	Order	Lactobacillales
	Family	Lactobacillaceae
	Genus	*Pediococcus*
	Species	*P. acidilactici*
First isolation	Lindner 1887	
Synonyms	*P. lindneri, P. cerevisiae, Streptococcus lindneri*[b]	
Habitats	Fermenting plant material (silage, cereal mashes, pickles), hey, fruits, salami	
Characteristics	Gram stain positive, non-spore forming, facultative anaerobic with lesser sensitivity to oxygen, oxidase and catalase negative, immotile, alpha-haemolytic	
Morphology	Cocci, often found in pairs or tetrads	
Growth conditions	$T_{opt.}$: 40 °C (35–53 °C) $pH_{opt.}$: 6.0–6.5 (4.2–8.5) Complex requirements: various vitamins, organic acids (nicotinic and pantothenic acid), biotin, riboflavin stimulates the growth[c]	
Fermented carbohydrates[d]	+:,cellobiose[b], fructose, glucose, galactose, mannose[b], ribose, xylose d: arabinose, lactose[b], raffinose, sucrose[b]	
Fermentation type	Homofermentative	
LA enantiomer[c]	DL	
Pathogenicity	No	
DNA G + C content	38–44 mol%	
Remarks	Some strains produce the bacteriocin pediocin	

+, 90 % or more of strains are positive; d, 11–89 % of strains are positive
[a]Holzapfel et al. (2009)
[b]Simpson and Taguchi (1995)
[c]Garvie (1986)
[d]Holzapfel et al. (2009)

Tang et al. 2013). Important features of *S. thermophilus* are summarized in Table 14.

S. thermophilus, like other streptococci that ferment carbohydrates, produce L-(+)-LA as well as minor amounts of acetic and formic acids, ethanol and CO_2 (Whiley and Hardie 2009).

2.4.5 *Saccharomyces cerevisiae*

Recently, there are reports about LA-forming yeasts such as *S. cerevisiae* (Dequin and Barre 1994; Praphailong and Fleet 1997; Bianchi et al. 2001; Lu et al. 2012) and other *Saccharomyces* species, *Zygosaccharomyces, Candida, Pichia and*

Table 14 Characteristics of *S. thermophilus*

Classification[a]	Kingdom	Bacteria
	Phylum	Firmicutes
	Class	Bacilli
	Order	Lactobacillales
	Family	Streptococcaceae
	Genus	*Streptococcus*
	Species	*S. thermophilus*
First isolation	Orla-Jensen 1919	
Synonyms	*S. salivarius* ssp. *thermophilus*	
Habitats	Dairy sources, heated and pasteurized milk, milk products	
Characteristics	Gram stain positive, non-spore forming, facultative anaerobic, oxidase and catalase positive, immotile, alpha-haemolytic, moderate thermophilic	
Morphology	Cells spherical or ovoid, forming pairs or chains	
Fermented carbohydrates[a]	+: fructose, glucose, lactose, mannose, sucrose d: galactose, raffinose, ribose, starch[b]	
LA enantiomer	L (+)	
Growth conditions	$T_{opt.}$: 45 °C, minimum 19–21 °C, maximum 52 °C $pH_{opt.}$: 6.5, no growth at pH 9.6 Requirements: B vitamins, some amino acids	
Pathogenicity	No	
DNA G + C content[c]	37–40 mol%	
Remarks	It is currently discussed whether the species *S. thermophilus* to be renamed in *Lactococcus thermophilus* to avoid confusion with the pathogenic part of the *Streptococcus* genus such as *S. pneumonia and S. pyogenes* Important species in the cheese manufacture	

+, 90 % or more of strains are positive; d, 11–89 % of strains are positive
[a]Whiley and Hardie (2009)
[b]Hardie (1986)
[c]Hardie and Whiley (1995)

Kluyveromyces that have been engineered to produce LA (Abdel-Rahman et al. 2013). Important features of *S. cerevisiae* are summarized in Table 15.

Carbohydrate Utilization

Under aerobic conditions, *S. cerevisiae* respire glucose, producing H_2O and CO_2. Under anaerobic conditions, cells ferment sugars to ethanol and CO_2. Galactose and fructose are shown to be two of the best fermenting carbohydrates. *S. cerevisiae* do not ferment pentoses such as arabinose, ribose and xylose and also disaccharides, e.g. lactose and cellobiose. Glucose oxidation under aerobic conditions provides more energy than fermentation. Therefore, the mass increases rate, and the cell division rate in oxidative decomposition of sugar is much higher than in

Table 15 Characteristics of *S. cerevisiae*

Classification[a]	Kingdom	Fungi
	Phylum	Ascomycota
	Subphylum	Saccharomycotina
	Class	Saccharomycetes
	Order	Saccharomycetales
	Family	Saccharomycetaceae
	Genus	*Saccharomyces*
	Species	*S. cerevisiae*
First isolation	Meyer *ex* Hansen 1883	
Synonyms[b]	Ca. 150 synonyms	
Habitats	Dairy products: wines, beer, fruits and berries, trees, cheese, kefir, sugar cane, man and other mammas	
Characteristics[b]	Facultative anaerobic, reproduction vegetative by budding, can form filaments and none or simple pseudohyphae, can be formed oval or round ascospores	
Morphology	Cells round or oval, 5–10 μm	
Growth conditions	$T_{opt.}$: 25–30 °C $pH_{opt.}$: 6.5–7.0, tolerate pH values as low as 1.5 Requirements: phosphorus, sulphur, amino acids methionine and cysteine, metals (magnesium, iron, calcium, zinc), biotin, pantothenate, prototrophic vitamins	
Fermented carbohydrates[b]	+: fructose, glucose, sucrose, raffinose d: galactose, maltose, melibiose, starch −: lactose, trehalose[c]	
LA enantiomer	D (−)	
Pathogenicity	No	
DNA G + C content[b]	38.8–42.0 mol%	
Remarks	Important in the baking and brewing, model organisms for genetic engineering	

+, 90 % or more of strains are positive; d, 11–89 % of strains are positive; −, 90 % or more of strains are negative
[a]Suh et al. (2006)
[b]Barnett et al. (1990)
[c]De Hoog et al. (2000)

fermentation. The ability of yeasts to use different sugars can differ depending on the oxygen conditions. So some strains cannot grow anaerobically on sucrose and trehalose. D-(−)-lactate formation is described by Stewart et al. (2013) (Fig. 6).

Experiments with *S. cerevisiae* under aerobic conditions demonstrated that during glucose consumption D-(−)-lactate forms as a result of methylglyoxal metabolism. The data suggest that increased glucose uptake by cells grown in a glucose-rich environment results in an increased generation of methylglyoxal with subsequent metabolism to D (−) lactate.

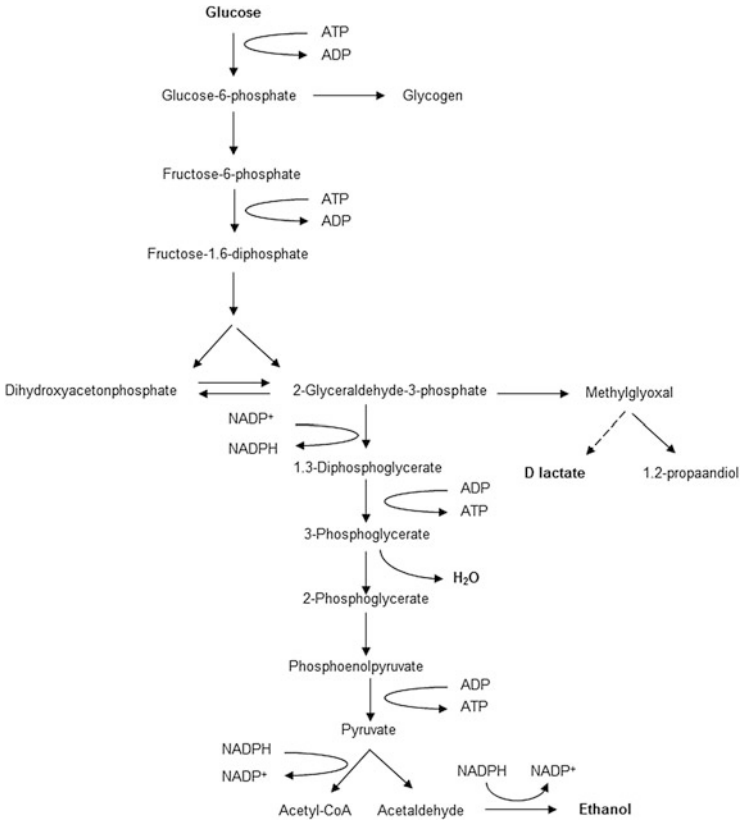

Fig. 6 D-(−)-Lactate production by *S. cerevisiae* (mod. Stewart et al. 2013)

2.4.6 *Rhizopus oryzae*

It is known that the mould in the genera *Rhizopus*, *Mucor* and *Monilia* form LA (Yadav et al. 2011). Currently, there are increasing reports on the production of LA by various species of *Rhizopus*, especially *R. oryzae* but also *R. arrhizus* (Bai et al. 2008; Taskin et al. 2012; Wu et al. 2011). *R. oryzae* produce a wide spectrum of metabolites, in the form of enzymes, esters, organic acids, volatile materials, polymers and bioalcohols. Biodiesel can also be produced. The fungus is a rich source of LA but also fumaric acid and to a better extent malic acid (Ghosh and Ray 2011). *R. oryzae* is a filamentous fungus belonging to the traditional Zygomycota (Hibbett et al. 2007). Its important features are summarized in Table 16.

Table 16 Characteristics of *R. oryzae*

Classification[a]	Kingdom	Fungi
	Subphylum	Mucoromycotina
	Order	Mucorales
	Family	Mucoraceae
	Genus	*Rhizopus*
	Species	*R. oryzae*
First isolation	Went and Prinsen Geerlings 1895	
Synonyms[b]	*R. arrhizus*, about more than 55 synonyms	
Habitats	Cereals, bread waste, compound fodder, vegetables, fruits, soil, polluted water	
Characteristics	Filamentous fungus, obligate aerobe	
Morphology[c]	– Fungus cobweb-like lawn with low slopes – Colonies are typically greyish to brownish – Rhizoid sparingly branched, up to 250 µm long, brownish – Sporangiospores brown, 1–2 mm high, up to 18 µm wide, angular, subglobose to ellipsoidal, with ridges on the surface, single or in tufts – Sporangia spherical, 50–250 µm in diameter, brownish-grey to black – Columella comprising 50–70 % of sporangium – Apophysis short, 3–12 µm high – Sporangiospores greyish green, angular, subspherical to ellipsoidal, longitudinally striate 6–8 × 4.5–5.0 µm – Chlamydospores single or in chains, spherical to ovoidal, 10–35 µm diameter, hyaline, smooth walled	
Growth conditions[d]	$T_{opt.}$: 30–35 °C, (5–7 °C, 44 °C) no growth at 45 °C $pH_{opt.}$: 5.5 (4–7) No special requirements: inorganic nitrogen sources, no amino acids and vitamin supplements	
Carbon sources[e]	Cellobiose, glucose, mannose, fructose, sucrose, starch, xylose, ethanol, glycerol, LA, fatty acids, oil	
Fermentation type	Heterofermentative	
LA enantiomer	L (+)	
Pathogenicity[e]	Generally regarded as safe, but same strains are also plant pathogen, opportunistic human pathogen	
Remarks	Used for food fermentation	

[a]Hibbett et al. (2007)
[b]CBS-Knaw (2014)
[c]De Hoog et al. (2000)
[d]Schmidt (2002)
[e]Meussen et al. (2012)

Formation of LA

In *R. oryzae*, all fermentable carbon sources are metabolized to pyruvate during glycolysis (Fig. 7).

The pyruvate is subsequently channelled to a number of pathways, including the pathways responsible for the formation of ethanol, lactate and fumarate. The dissolved oxygen in the medium influences the flow of pyruvate. Under anaerobic

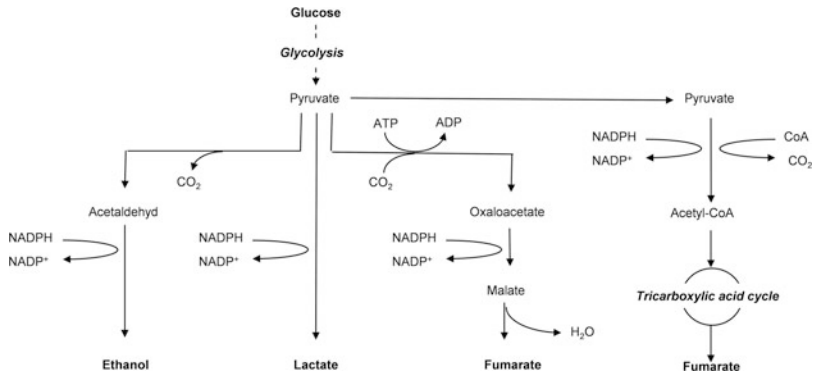

Fig. 7 Fermentation routes of glucose in *R. oryzae* (mod. Meussen et al. 2012)

conditions, the carbon flow is directed towards the formation of ethanol, while under aerobic conditions, with excess of carbon substrate, the flow is directed towards organic acid production (Skory et al. 1998; Meussen et al. 2012). With a mutagenizing strain, they could express almost a tenfold increase in LA production compared to the parental strain. Also the formation of L-(+)-LA is possible by strains of *R. oryzae* or genetically modified strains (Bai et al. 2004; Park et al. 2004). *R. oryzae* is widely studied as a commercially perspective producer of L-(+)-LA (Miura et al. 2003; Yin et al. 1997; Yamane and Tanaka 2013), because the fungus cells possess better resistance to high concentrations of accumulated LA (Hamamci and Ryu 1994; Schepers et al. 2003). Moreover the cells need lower nutrient requirements compared to the commonly used bacterial producers (Hujanen et al. 2001; Kwon et al. 2000). The use of *R. oryzae* in immobilized form is one of the most efficient approaches to improve the LA production process for long-term acid production (Tay and Yang 2002; Efremenko et al. 2006; Yamane and Tanaka 2013).

2.4.7 *Escherichia coli*

There are many challenges for the industrial production of LA, and satisfying all these requirements is very difficult through the traditional use of LAB. Therefore, improving LAB via gene modification and using other microorganisms (e.g. *E. coli*) and yeast for LA production via gene modification have become an essential and interesting research area (Grabar et al. 2006; Okano et al. 2010). Several research activities are directed towards the recombinant improvement of LA yield and the optical purity since *E. coli* produces a mixture of organic acids and other metabolites (Zhou et al. 2012; Mazumdar et al. 2013; Zhao et al. 2013a). Important features of *E. coli* are summarized in Table 17.

Table 17 Characteristics of *E. coli*

Classification[a]	Domain	Bacteria
	Kingdom	Eubacteria
	Phylum	Proteobacteria
	Class	Gammaproteobacteria
	Order	Enterobacteriales
	Family	Enterobacteriaceae
	Genus	*Escherichia*
	Species	*E. coli*
First isolation	Theodor Escherich 1885	
Synonyms	No	
Habitats	Human and warm-blooded animal intestines	
Characteristics	Gram negative, non-spore forming, aerobic and facultative anaerobic, motile or immotile, catalase positive, oxidase negative	
Morphology[a]	Straight, cylindrical rods with rounded end, single or in pairs, diameter 1.1–1.5 µm, length 2.0–6.0 µm, peritrichous flagella	
Growth conditions	$T_{opt.}$: 37 °C (7.5–49 °C) $pH_{opt.}$: 7.0 (5–9) Requirements: no special supplements are necessary	
Fermented carbohydrates	+: arabinose, glucose, lactose, maltose, mannose, xylose[b] d: raffinose, sucrose	
LA enantiomer	D (−)	
Pathogenicity	Most nonpathogenic, but some serotypes or clones are human pathogen (EHEC, STEC, VTEC), animal pathogen	
DNA G + C content	48.5–52.1 mol%	
Remarks	Important host organism in the molecular biology	

+, 90 % or more of strains are positive; d, 11–89 % of strains are positive
[a]Scheutz and Strockbine (2009)
[b]Devriese and Pot (1995)

Lactate Formation

E. coli can grow both under aerobic and anaerobic conditions. Like other species of the family Enterobacteriaceae, *E. coli* ferments glucose anaerobically via pyruvate to various acids and gas. Pyruvate can be formed either via glycolysis or via the EMP or the Entner-Doudoroff (ED) pathway (Fig. 8). However, the ED pathway is by *E. coli* of minor importance, because the enzymes of the ED pathway are only induced at the presence of gluconate, glucuronate, galacturonate or idonate (Eisenberg and Dobrogosz 1967). The resulting pyruvate is converted to D-(−)-lactate, acetate, succinate and formate via so-called mixed-acid fermentation. Part of the formic acid is split into equal amounts of CO_2 and H_2. The sum of the equation is (Schlegel 2007)

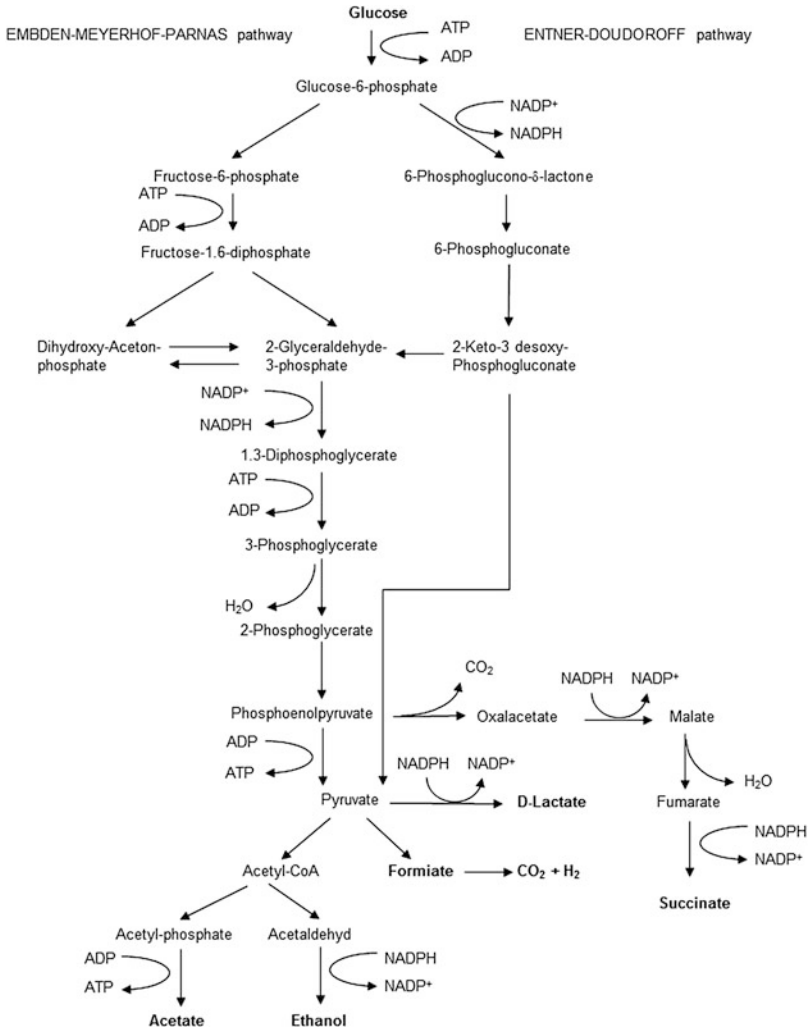

Fig. 8 Anaerobe fermentation of glucose by *E. coli*

$$C_6H_{12}O_6 \rightarrow 0.84\,C_3H_6O_3 + 0.44\,C_2H_4O_2 + 0.42\,C_2H_5O + 0.29\,C_4H_6O_4 + 0.02\,CH_2O_2 + 0.44CO_2 + 0.43\,H_2 + ATP$$

Approximately 80 % of the glucose is fermented by these pathways, and the other 20 % are metabolized by the oxidative pentose phosphate pathway (Fuhrer et al. 2005).

Table 18 Characteristics of *L. paracasei* ssp. *paracasei*

Classification[a]	Kingdom	Bacteria
	Phylum	Firmicutes
	Class	Bacilli
	Order	Lactobacillales
	Family	Lactobacillaceae
	Genus	*Lactobacillus*
	Species	*L. paracasei*
	Subspecies	*L. paracasei* ssp. *paracasei*
First isolation	Collins, Phillips and Zanoni 1989	
Synonyms	*Lactobacillus casei* ssp. *alactosus* Mills and Lessel 1973 *Lactobacillus casei* ssp. *pseudoplantarum* Abo-Elnaga and Kandler 1965	
Habitats	Dairy products, sewage, silage human, and clinical sources	
Characteristics	Gram stain positive, facultative anaerobic, catalase negative, immotile	
Morphology	Rods often with square end, occurring singly or in chains	
Growth conditions	$T_{opt.}$: 30 °C (5–45 °C) $pH_{opt.}$: 6.5 Requirements: individually various complex nutritional requirements for peptides, amino acids, nucleotides, vitamins and fermentable carbohydrates	
Fermented carbohydrates[b]	+: cellobiose, fructose, glucose, galactose, mannose, ribose, xylose d: arabinose, lactose, raffinose, sucrose	
Fermentation type	Facultative heterofermentative	
LA enantiomer	L (+)	
Pathogenicity	No	
DNA G + C content[c]	45–47 mol%	

+, 90 % or more of strains are positive; d, 11–89 % of strains are positive
[a]Hammes and Hertel (2009)
[b]Holzapfel et al. (2009)
[c]Hammes and Vogel (1995)

3 Organic Lactate-Forming Bacteria

Various organic lactates are formed by LAB, such as 1,4-piperazinium-(L,L)-dilactate (Kamm et al. 1997; Richter et al. 2001), imidazole-(L)-lactate (Kamm et al. 1999), hexamethylenediamine-(L,L)-dilactate (Gutmacher 2008) and lysine-(L)-lactate (Leiss et al. 2010). Piperazinium-(L,L)-dilactate, imidazole-(L)-lactate (Kamm et al. 1999) and hexamethylenediamine-(L,L)-dilactate are applied as intermediates for the production of polylactic acid (Kamm et al. 1999, 2000). These lactates are formed by means of strains of *Lactobacillus paracasei* ssp. *paracasei*. *I*mportant features of *L. paracasei* ssp. *paracasei* are summarized in Table 18.

LA is produced through facultative heterofermentation, which means cells of the strain ferment hexoses and pentoses (see Sect. 2.1). Hexoses are fermented by the

EMP glycolytic pathway to L-(+)-lactate. The same strains, which are formerly described as *L. pseudoplantarum*, produce DL-LA (Hammes and Hertel 2009). Pentoses enter this pathway and are fermented to LA and acetic acid.

4 Platform Chemical Lactic Acid

Currently there are criteria for a platform chemical, such as multiple product applicability, high-volume product and potential industrial scaleup (Bozell and Petersen 2010). LA is widely used in the food, cosmetic, pharmaceutical and chemical application, such as lactic acid derivatives as dyeing assistants, and has received increased attention for use as a monomer for the production of biodegradable PLA (Datta et al. 1995; Kamm et al. 1997, 2000; Nampoothiri et al. 2010; Castillo Martinez et al. 2013). LA is one of the most interesting intermediates for the synthesis of industrial relevant bio-based compounds based on carbohydrates, and it was foreseen as a platform chemical for the production of several downstream chemicals. Lactic acid undergoes ready esterification to give lactate esters, of interest as new bio-based 'green' solvents (Kamm et al. 2008). Lactate esters have many potential markets as non-toxic replacements for halogenated and toxic solvents. The use of esters, e.g. ethyl lactate and butyl lactate as solvents for cellulose lacquers or poly(vinyl) compounds, is important, and a great variety of esters have been recommended for use as plasticizers in polymers. Catalytic reduction of lactic acid leads to propylene glycol, which can be further dehydrated to give propylene oxide. Alternatively, lactic acid can be dehydrated to give acrylic acid and esters, but in practice this conversion proceeds in low yield (Walkup 1991).

The global lactic acid demand was estimated to be 714.2 kilo tons in 2013, which is expected to reach 1,960.1 kilo tons by 2020, growing at a compound annual growth rate of 15.5 % from 2014 to 2020 (SpecialChem 2014). Growth in demand for LA and its salts and esters in industrial applications will be driven mainly by LA-based biodegradable polymers and, to a lesser degree, lactate solvents (Abdel-Rahman et al. 2013; Taskila and Ojamo 2013).

5 Intermediate and Speciality Chemicals: Organic Lactates

Aminium lactates, such as piperazinium dilactate, imidazole lactate and hexamethylenediamine dilactate, are applied as intermediates for the production of polylactic acid (Kamm et al. 2000) and for the manufacture of high purity lactic acid (Kamm et al. 1999). Aminium lactates can be applied directly as constituents of pharmaceutical and cosmetic products as well. Piperazine lactate

has anthelmintic activity (Chatterjee et al. 1997). Imidazole lactate is useful as a topical antilipolytic (Carreras Ginjaume 1985) and lysine lactate can be applied as component in skin lotions (Parab 1995). The antimicrobial activities of protic ionic liquids with lactate ion were investigated intensively (Pernak et al. 2004).

6 Biotechnological Production of LA

Biotechnological processes and bio-based products are an interesting alternative compared to classical ones of chemistry. The so-called white biotechnology points to an emerging field in biotechnology with immense potentials via utilization of biocatalysts for the manufacture of industrial products. The goal is to develop a fermentation process based on the substitution of expensive nutrient supplements by cheaper materials from renewable resources due to their main proportion of the whole process costs (Akerberg and Zacchi 2000; Okano et al. 2010). Depending on the further processing of the LA (e.g. for bioplastics), the separation of impurities after fermentation is a major process cost too (Fitzpatrick et al. 2003; Ryu et al. 2012). Therefore an optimization is necessary to find a balance between the substitution of expensive nutrients and the limitation of interfering or undesirable components of natural raw materials, respectively.

The worldwide research is advancing focused on the use of renewable raw materials as carbon substrates as well as nutrient additive resources. In this context, there is a strong interest to reduce costs for raw materials and to use renewable resources.

With respect to the above-mentioned cost aspect of bioprocess feedstock, the utilization of residues and waste materials (Pintado et al. 1999; Huang et al. 2005; Bischoff et al. 2010; Ouyang et al. 2013; Tang et al. 2013) and agricultural by-products (Thomsen 2005; John 2009; Alonso et al. 2011; Li et al. 2012) became the focus of public attention.

LA was produced worldwide at first from glucose or pure starch on fermentative ways (Richter and Berthold 1998). First efforts for developing bioconversion processes for the production of LA directly from agricultural starchy feedstock were published by Shamala and Sreekantiah (1987). During the last years, starchy hydrolysates obtained from agricultural resources like corn or barley (Linko and Javanainen 1996; Oh et al. 2005; Venus and Richter 2006), cassava (Xiaodong et al. 1997; Bomrungnok et al. 2012), wheat (Hetenyi et al. 2010), rye (Otlewska et al. 2012), potatoes (Zhang and Jin 2010; Bilanovic et al. 2011) and sago (Nolasco-Hipolito et al. 2002) were also tested on their suitability as substrates for LA fermentation.

Lignocellulosic biomass represents the most abundant global source of biomass, and for this reason it has been largely utilized in many applications (Taherzadeh and Karimi 2007). Lignocellulosic materials can be used to obtain sugar solutions that may be usefully exploited for the production of LA through the following steps: (a) pretreatment to break down the lignocellulosic structure, (b) enzymatic

hydrolysis to depolymerize lignocellulose to fermentative sugars, (c) sugar fermentation to LA by LAB and (d) separation and purification of LA (Moldes et al. 2006, Abdel-Rahman et al. 2011). In recent years, one of the most used processes to obtain LA from lignocellulosic materials is the simultaneous saccharification and fermentation (John et al. 2009; Qi et al. 2011; Zhao et al. 2013b), which is able to prevent enzyme inhibition by the product (Gullon et al. 2007; Castillo Martinez et al. 2013).

LAB need, besides the carbon source, also a source of nitrogen and other nutrients and phosphorus. The latter is available when inorganic phosphate salts are added to the medium. The demand for nitrogen cannot be covered by inorganic salts only. LAB need also a series of nitrogen-containing nutrients (amino acids, peptides, etc.) for growth, and therefore, the medium has to be supplied by complex protein hydrolysates (yeast extract, peptone, etc.). The protein extracts mentioned are very expensive, and their substitution by low-priced nutrient extracts is necessary when a large-scale production is planned. A useful combination of green biomass processing for the production of fodder pellets and the utilization of the pressed juice for the LA fermentation was described by Andersen and Kiel (2000) and Vodnar et al. (2010). The use of date juice together with different nitrogen sources as a substrate for LA production was investigated by Nancib et al. (2001).

7 Future Perspectives

Although LA production by LAB is very efficient, further improvements in the process can help make it more cost competitive with petroleum-based polymers for PLA production. Environmentally friendly, 'green' solvents are another potential area for lactic acid derivatives, particularly lactate esters of low-molecular-weight alcohols such as ethyl, propyl and butyl lactate (John et al. 2007; Delgado et al. 2010). From that perspective the lactate esters have also further applications in order to run alternative downstream technology (Kamble et al. 2012) and PLA polymerization process (Marques et al. 2012).

Yield and purity of the LA produced are currently limited by many factors including the production of both L- and D-LA via L-lactate dehydrogenase and D-lactate dehydrogenase, respectively, low yield due to by-product formation, use of nutritionally rich medium, high risk of bacteriophage infection that results in cell lysis and subsequent cessation of LA production (Abdel-Rahman et al. 2013). In addition to the previously used LAB and LA-producing microorganisms, these organisms are interesting for the production of LA that were until now get low attention such as microalgae and cyanobacteria.

Through different approaches, these defects can be partially remedied today. The usage of mixed strains and/or development of phage-resistant strains can prevent bacteriophage infection (Hassan and Frank 2001).

Various studies have investigated methods to overcome some problems in the field of metabolic engineering of the strains, e.g. improvement of optical purity via

the deletion of either D- or L-LDH genes (Kyla-Nikkila et al. 2000) and increased LA yields through the reduction of by-product levels by the deletion of genes encoding pyruvate formate lyase (formic acid production), alcohol dehydrogenase (ethanol production) and/or acetate kinase (acetic acid production) (Zhou et al. 2003a).

Moreover, the development of bacterial strains producing LA on chemically defined media (Zhou et al. 2003b) and strains improving blocking steps in the phage life cycle (Allison and Klaenhammer 1998; Forde and Fitzgerald 1999) is advanced.

Another way to more effective LA formation is the search for organisms that can tolerate high pH values. Alkaliphilic LAB strains may be promising producers of LA due to their tolerance to high pH levels that would minimize contamination problems during processing. Calabia et al. (2011) isolated an alkaliphilic *Lactobacillus halophilus* from a marine environment that produced 65.8 g/L of L-LA at pH 9.0. By comparison, the strategy of NatureWorks as the main global PLA producer is directed on the yeast fermentation at lower pH, thereby significantly reducing the use of calcium hydroxide and sulphuric acid, in turn resulting in significantly lower quantities of gypsum together with less energy demand for the entire process (Vink et al. 2010).

Also not yet used for the formation of LA are organisms such as microalgae and cyanobacteria. These photosynthetic microorganisms offer an alternative LA production approach and would allow carbohydrate feedstock costs to be eliminated. It has long been known that some microalgae have the ability to convert the starch they accumulated under light and aerobic conditions into organic matter, such as LA, ethanol, acetic acid and formic acid under dark and anaerobic conditions (Hirayama and Ueda 2004; Oost et al. 1989). There are also reports about the LA production by the microalgal species *Nannochlorum* sp. 26A4 from about 26 g/L D-LA production with an optical purity of 99.8 % from their starch (40 % content per dry weight) at yield of 70 % under dark and anaerobic conditions (Hirayama and Ueda 2004).

New strains with new properties alone will not lead to more efficient production of LA, but only in interaction with new raw materials, progress in fermentation technology as well as downstream processing development. Because of the relatively low price of LA, one of the major challenges in its large-scale fermentative production is the cost of the raw material. Lactic acid can be produced from a wide spectrum of carbon sources including starchy materials, many food industry by-products (e.g. molasses, whey), agro-industrial residues and by-products (e.g. lignocellulose hydrolysates, cottonseed hulls, corn cob, corn stalks, wheat bran, brewer's spent grains) and various other renewable resources. Together with the need of low-cost carbon, there is an additional demand of suitable supplements, which should not cause additional costs and problems in view of impurities. Therefore, the kind of nutrients as well as the optimization of their concentration is essential. It is likely that one of the future trends in lactic acid production will end up in mixtures of different low-cost raw materials in order to avoid the use of expensive complex supplements (Taskila and Ojamo 2013; Koutinas et al. 2014).

Besides the strain optimization and alternative raw materials, the transition from traditional batch including repeated batch and fed-batch fermentation to continuous mode fermentation (Dey and Pal 2013; Gao and Ho 2013) with cell recycle (Venus 2009; Wee and Ryu 2009; Lee et al. 2014) as solutions with free cells and the use of immobilized cells in different reactor types (fixed or fluidized bed) could lead to further performance improvement. The number of downstream processing steps strongly influences the quality and the price of the product. Thus the total costs are determined mainly by the purification rather than by LA production using fermentation (Reimann 2006). Open sources provide only limited data about industrial product recovery processes, but the main technology steps are known for large-scale production of carboxylic acids and ongoing research activities are widely discussed (López-Garzón and Straathof 2014). If the disadvantages of traditional fermentation and recovery process are overcome combined with the huge amount of gypsum as a by-product, significant progress for lactic acid production can be expected in the near future.

Furthermore methods for combining the fermentation of lactic acid and production of chemical sequence products derived from lactic acid are required for the development of intermediates and speciality chemicals. A worthwhile approach could be the direct fermentation on organic lactates, such as substituted aminium lactates.

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